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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/712,642 | 11/12/2003 | Gloria C. Li | 1747 / 55672-AA-PCT-US/JP | 8975 |

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| EXAMINER | |
|---|---|
| ZARA, JANE J | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/712,642 | LI ET AL. | |
| | Examiner | Art Unit | |
| | Jane Zara | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *27-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11-2-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This Office action is in response to the communication filed 11-2-07.

Claims 27-40 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11-2-07 has been entered.

### *Response to Arguments and Amendments*

*Withdrawn Rejections*

Any rejections not repeated in this Office action are hereby withdrawn.

### *Maintained Rejections*

Claims 28-33, 35-38 and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method of increasing a target cell's susceptibility to DNA damaging agents comprising the administration of

antisense that inhibit the expression of human Ku70, and for being enabling for the in vivo inhibition of Ku70 expression and treatment of tumors comprising the direct administration, to a tumor, of full length antisense of human Ku70, does not reasonably provide enablement for the full scope of in vivo methods claimed, comprising administration by any route or means of antisense to human Ku70, and further whereby treatment has been provided in an organism, for the reasons set forth in the prior Office actions of 4-13-06 and 1-11-07.

Applicant's arguments filed 11-2-07 regarding the scope of enablement rejection have been fully considered but they are not fully persuasive.

The claims are drawn to pharmaceutical compositions and methods of treating tumors in a subject comprising administration of a full length antisense of human Ku70 by any means or route of administration, and which antisense is optionally expressed from an adenoviral vector under control of a heat shock promoter, and inhibits the expression of human Ku70.

Applicant argues that the specification provides adequate guidance for the full scope of the claimed invention and such support is found in various places of the instant disclosure, including Figure 13, pages 12 and 83, and in the prior art, as wet forth in the October 13, 2006 argument, which pointed out success by others involving the adenoviral vector delivery of antisense under the control of a heat shock promoter.

Contrary to Applicant's assertions, neither the teachings provided in the instant disclosure, nor those in the prior art provide adequate guidance for the full scope of the claims. The specification teaches an increase in radiation and chemotherapeutic

sensitivity in Ku70 cells obtained from Ku70 knockout mice. One skilled in the art would not accept on its face the examples given in the specification of gene ablation experiments and further characterization of cells derived from such knockouts as being correlative or representative of the ability to inhibit the expression of Ku70 in appropriate target cells in vivo using antisense and further whereby treatment effects are provided.

Moreover, delivery of full length antisense using any route of administration, including systemic administration, is a highly unpredictable endeavor. The guidance provided of in vitro delivery and inhibition of target gene expression is not representative or correlative of the ability to treat any tumor anywhere in the body using the instantly claimed full length antisense via any route of administration. What's more, the success obtained with other therapeutic agents, targeting other genes, including using adenoviral vectors with a heat shock promoter, does not adequately predict success for the in vivo inhibition of the instant target gene (Ku70) using full length antisense of human Ku70, via any route of administration.

Contrary to Applicant's assertions, the efficacy of an antisense targeting a different target gene is not predictive of the ability of a different and distinct antisense (e.g., targeting a different target gene) to provide treatment effects in a subject. The efficacy of both the antisense and an appropriate delivery device must be tested empirically for satisfying enablement requirements for the full scope claimed, of providing treatment effects for any tumor in an organism by administering the full length antisense to human Ku70 via any route of administration.

For these reasons, in instant rejection is maintained.

*New Rejections*

Applicant's arguments with respect to the obviousness rejection have been considered but are moot in view of the new ground(s) of rejection set forth below.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 27, 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reeves et al (J. Biol. Chem., Vol. 264(9): 5047-5052, 1989) and Milner et al (Nature Biotech. 15: 537-541, 1997), the combination in view of Taniguchi et al (Genomics 35: 129-135, 1996), Reed et al (Proc. Natl. Acad. Sci., Vol. 87, pages 3660-3664, 1990) and Au-Young et al (USPN 5,773,580) insofar as the claims are drawn to compositions and methods for increasing a target cell's sensitivity to DNA damaging agents in vitro or upon direct administration comprising the administration of an antisense oligonucleotide, optionally in an adenoviral expression vector comprising a heat shock promoter, that specifically hybridizes with a nucleic acid encoding a DNA dependent protein kinase subunit (Ku70), which antisense inhibits the expression of the target Ku70 subunit.

Reeves et al (J. Biol. Chem., Vol. 264(9): 5047-5052, 1989) teach the cloning, characterization and polynucleotide sequence encoding human DNA-PK subunit Ku70,

and the binding of Ku70 to the ends of double stranded DNA in a complex with Ku80 (see especially figure 4 on p. 5050 and the text on p. 5047).

Milner et al (Nature Biotech. 15: 537-541, 1997) teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the expression of a target nucleic acid of known nucleotide sequence in vitro (See especially figures 5-7 on pages 539-540).

The primary references of Reeves et al and Milner et al do not teach methods for increasing a target cell's sensitivity to DNA damaging agents in vitro comprising the administration of an antisense oligonucleotide specifically targeting a nucleic acid encoding Ku70, and which antisense is in an adenoviral expression vector, operably linked to a heat shock promoter.

Takiguchi et al (Genomics 35: 129-135, 1996) teach the role of mouse and human DNA-PK (comprising the subunits Ku70, Ku80 and DNA-PK catalytic subunit) in DNA repair, and an increase in a cell's sensitivity to DNA damaging agents with loss of DNA-PK function. Takiguchi teaches the crucial role of Ku70 in DNA double stranded repair, and the importance in studying the subunits of DNA-PK in human diseases and in immunogenesis (see text on p. 129; p. 133-134).

Reed et al (Proc. Natl. Acad. Sci., Vol. 87, pages 3660-3664, 1990) teach the inhibition of tumor growth in mice comprising the delivery of an expression plasmid comprising the full length antisense sequence to Bcl2 (see the abstract, introduction on p. 3660, Fig. 1 on p. 3661, fig. 3 on p. 3662, and fig. 4 on p. 3663).

Au-Young et al (USPN 5,773,580) teach pharmaceutical compositions comprising antisense oligonucleotides for inhibiting a known target gene, as well as teaching adenoviral expression vectors comprising antisense oligonucleotides and ribozymes, which oligonucleotides are operably linked to regulatory elements including an inducible (heat shock) promoter (see esp. col. 10-11, 20-21).

It would have been obvious to one of ordinary skill in the art to design and utilize antisense oligonucleotides to inhibit the expression of Ku70 in vitro because its nucleotide sequence had been taught previously by Reeves et al, Milner et al and Reed et al teach the ability to design and assess antisense oligonucleotides, including full length antisense in an appropriate expression plasmid for their ability to inhibit the expression of a target gene of known nucleotide sequence using routine screening assays that are well known in the art (see Milner at pages 539-540). Milner et al additionally teach methods of designing and evaluating antisense which target different regions of a target gene of previously disclosed sequence for their ability to inhibit a target gene in vitro. One of ordinary skill in the art would have expected that the methods of designing and assessing antisense oligonucleotides for inhibiting a target gene of known sequence, which were taught by Milner et al, to be routine for a previously characterized target gene, would successfully be used to identify numerous antisense oligonucleotides human DNA dependent protein kinase subunits, including Ku70. One would have expected that, upon target cell delivery, full length antisense to a known target gene, and in an appropriate expression plasmid, would provide for target gene inhibition because Reed et al have taught the inhibition of a known target gene

upon administration and successful delivery and expression of the full length antisense construct.

It would have been obvious to one of ordinary skill in the art to insert antisense oligonucleotides into an appropriate expression vector, operably linked to an inducible promoter including a heat shock promoter, because such expression systems have been used routinely in the art for expression of nucleic acid constructs including antisense and ribozymes in an appropriate target cell, as taught previously by Au-Young et al. One of ordinary skill in the art would have been motivated to operably link an antisense oligonucleotide to an inducible promoter in an appropriate expression vector, including an adenoviral vector, in order to control the conditions of expression of the operably linked antisense, and in order to control conditions for antisense expression and subsequent inhibition of the antisense's target gene in an appropriate target cell.

One of ordinary skill in the art would have been motivated to target and inhibit the expression of the various subunits of DNA-PK, including Ku70, in order to increase a target cell's sensitivity to DNA damaging agents because Taniguchi et al teach the relationship between increasing cell radiosensitivity or loss of DNA repair function, and loss of functional DNA-PK. One of ordinary skill in the art would have been motivated to inhibit the expression of Ku70 in order to increase a target cell's sensitivity to DNA repair because it was well known in the art that Ku 70 is involved in double stranded DNA repair and it was also well known that strand repair occurs in cells following DNA damage (e.g. strand breaks). One of ordinary skill in the art would have expected that a cancer cell would undergo DNA repair after its exposure to DNA damaging agents.

And one of ordinary skill in the art would be motivated to undermine a cancer cell's ability to repair DNA after treating it with DNA damaging agents in order to eventually undermine that cancer's ability to survive.

One of ordinary skill in the art would have expected that by utilizing appropriate conditions for expression (e.g. induction by heat), the antisense targeting DNA-PK would be expressed upon induction of the heat shock promoter because such induction systems as heat shock promoters have been routinely used as described by Au-Young et al. One of ordinary skill in the art would have been motivated to induce expression of antisense and ribozymes under desired conditions (e.g. upon exposure heat) because induction is a way of controlling the conditions for increased expression of the operably linked antisense and ribozymes, and also a way of controlling the subsequent inhibition of target gene expression following expression of these antisense. In this way, increasing a cell's sensitivity to DNA damaging agents is in turn induced following heat treatment and expression of antisense. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

***Double Patenting***

Claims 27, 39 and 40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 15, 16 and 18-22 of copending Application No. 09/750,410 for the reasons of record set forth in the Office actions mailed 4-13-06 and 1-11-07.

Nor arguments were made addressing this rejection.

***Conclusion***

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**Jane Zara**
**1-31-08**

TC1600

JANE ZARA, PH.D.
PRIMARY EXAMINER